Genetic and genomic perspective to understand the molecular pathogenesis of keratoconus

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Keratoconus (KC; Mendelian Inheritance in Man (OMIM) 14830) is a bilateral, progressive corneal defect affecting all ethnic groups around the world. It is the leading cause of corneal transplantation. The age of onset is at puberty, and the disorder is progressive until the 3rd–4th decade of life when it usually arrests. It is one of the major ocular problems with significant social and economic impacts as the disease affects young generation. Although genetic and environmental factors are associated with KC, but the precise etiology is still elusive. Results from complex segregation analysis suggests that genetic abnormalities may play an essential role in the susceptibility to KC. Due to genetic heterogeneity, a recent study revealed 17 different genomic loci identified in KC families by linkage mapping in various populations. The focus of this review is to provide a concise update on the current knowledge of the genetic basis of KC and genomic approaches to understand the disease pathogenesis.

Key words: Disease pathogenesis, genetic heterogeneity, genetics and genomics, genome-wide association study, genomic loci, keratoconus, linkage mapping, molecular mechanisms, whole exome-genome sequencing

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The completion of the Human Genome Project and the International HapMap Project, coupled with new technologies like, large-scale genome-wide association studies (GWAS) and in-depth next-generation sequencing (NGS) have allowed researchers to identify genetic variations linked to many human diseases. These new discoveries are likely to provide insight into the genes and gene variations involved in the disease which may lead to more accurate disease risk assessment and eventually to a personalized therapy.

Genetics and Genomics of Keratoconus

KC is a corneal ectasia that results in the conical shape of the cornea. It is no longer thought to be entirely non-inflammatory as was described in the past. With different diagnostic criteria utilized in a variety of studies, the prevalence of KC varies from 8.8 to 54.4 per 100,000. The mean age of onset of KC is 39.3 years.[1] It is a multifactorial disease, does not exhibit classical Mendelian patterns of inheritance, characteristically involves several genes that interact in complex mode with multiple environmental factors and systemic conditions.[2],[3],[4],[5],[6] It has been proved beyond doubt that KC is a complex heterogeneous disorder with multifactorial etiology, associated with genetic (familial inheritance) and environmental factors like contact lens wear, chronic eye rubbing, and atopy of the eye.[2],[7],[8] The biology of KC and cellular changes in cornea were described in Table 1.

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KC is well-documented as a genetic predisposition with increased incidence in familial and monozygotic twins.[2],[9],[10] Most of the KC patients are sporadic and family history is reported in 6–10% of patients.[11],[12] So far the modes of disease inheritance in KC families are dominant and recessive, but in autosomal dominant inheritance, the disease shows incomplete penetrance with variable phenotype.[12] In addition, cellular pathways (inflammatory, apoptosis) are involved in the development of KC.[13] The exact cause of KC is uncertain, but has been associated with abnormal enzyme activity within the

Table 1: Cellular level changes in cornea found in patients with keratoconus

Parts of cornea	Pathogenic features of keratoconus
Epithelium	The corneal epithelium shows elongated superficial cells, arranged in a whorl-like fashion[9-12] Iron particle deposition (Fleischer's ring) [13,14] Nerve fibers are thickened, visible, and less in number[15]
Bowman's membrane	Ruptures/breakages resulting in direct contact between epithelial and stromal cells[16,17]
Stroma	Thinning of stroma due to reduced number of lemellae and keratocytes Vertical lines/striae in the deeper layers of stroma[2,3,9,10,18]
Descemet's membrane	Ruptures and folds in keratoconus results in a porous membrane which leads to loss of endothelial cells[11,17]
Endothelium	Unaffected in keratoconus or may demonstrate pleomorphisms and elongation of cells[2]

cornea.[14] A genetic link seems likely, as the incidence rate is greater if a family member has been diagnosed. Due to genetic heterogeneity, different genomic loci have been identified in KC families by linkage analysis.[15],[16],[17],[18],[19]

Candidate gene approach

Many eye diseases have a genetic basis and researchers often focus in identifying the genes responsible, for enabling early detection and possible treatments. Hence, the basic idea is to analyze the presence of the gene mutations in affected patients when compared with normal unaffected individuals. The candidate gene approach thus directly tests the effects of mutations located in specific genes for their "association" to the disease. The potential candidate genes in KC were selected based on the previously published association with other corneal disorders (corneal dystrophies) and their known functions in the eye development. Here, we discuss some of the candidate genes related to KC phenotype and their role in the pathogenesis.

Visual system homeobox 1 is a protein that in humans is encoded by the *VSX1* gene, plays a role in craniofacial and ocular development. *VSX1* gene missense mutations (R166W and L159M) were identified in KC patients.[20] VSX1 is a member of the paired-like homeodomain transcription factors (TFs) which may regulate expression of the cone opsin genes during the embryonic development.[21],[22] Although it plays a role in the development of retinal bipolar interneurons,[23] no expression has been detected in the mouse and human cornea.[24] Animal models of VSX1 also did not support a role in cornea.[25] Thus, although *VSX1* mutations are responsible for a very small fraction of KC cases[20] it may not play a major role in the pathogenesis of KC.[25],[26]

The dedicator of cytokinesis 9 (*DOCK9*) is a possible candidate gene, which encodes a member of the DOCK protein family that possesses guanosine triphosphate/guanosine diphosphate (GTP/GDP) exchange factor activity and specifically activates G-protein CDC42 involved in intracellular signaling networks. The expression patterns were observed in keratoconic and non-keratoconic corneas as well as in lymphoblastoid cell lines. Recently, mutation (Gln754His) was reported through sequencing candidate genes in a previously identified linkage locus, 13q32.[27] A mutation screening of eight candidate genes within the 13q32 locus identified three different sequence variants in the *DOCK9* gene. This locus contains additional genes, *IPO5* (importin 5) and STK24 (serine/threonine kinase 24).[28] All these three genes are expressed in the human cornea but detailed expression analyses are required to determine their role in KC pathogenesis.[28] Another gene called transforming growth factor beta-induced (*TGFβI*) gene which is a cytokine, is responsible for many dominant corneal dystrophies.[29] It is a potent regulator of the extracellular matrix formation, during tissue injury and repair. Recently, a novel nonsense mutation of *TGFβI* (G535X), was observed in a Chinese patient with KC.[29] Though in contrast mouse embryos that lack TGFβ1, have normal signs of ocular development.[30] TGFβ1 is well-known to be involved in corneal fibrosis and scar formation.[31] An increase in TGFβ pathway markers was seen in severe KC cases.[32]

Oxidative stress has been demonstrated to be involved in several human diseases including corneal diseases.[33] *SOD1* maps to the 20p11.2 and encodes a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals and provides a defense against oxygen toxicity.[33] A unique genomic 7 bp deletion within intron 2 close to the 5' splice junction of the antioxidant related *SOD1* gene was identified in three patients with KC.[34] Previously, *SOD1* gene mutations were identified in familial amyotrophic lateral sclerosis (ALS) patients, but no significant corneal phenotype was noted.[34],[35] However, recently, several reports have shown the high levels of oxidative stress markers such as cytotoxic byproducts, mitochondrial DNA damage in KC corneas.[33],[36]

Another hypothetical explanation for KC pathogenesis could be related to underlying changes in the corneal collagen structure, function and/or during embryonic development. However, *COL4A3* and *COL4A4* mutation analysis revealed no pathogenic variants in 107 patients with KC. Interestingly, significant allele frequency (genetic variants) was found in KC cases that are D326Y variant in *COL4A3* and M1237V and F1644F in *COL4A4*.[37] Another mutation study on 15 Ecuadorian families with KC identified missense mutations but none of them segregated in with family members.[38] In parallel 50 patients were investigated for *COL8A1* and *COL8A2*, but yet again no pathogenic mutation was detected.[39] Thus, the role of collagen mutations remains debatable. Recent investigation has shown the keratocyte apoptosis observed in keratoconic cornea, emphasized the role of apoptotic processes in the pathogenesis.[40] The apoptosis related genetic risk factor for atopic dermatitis is filaggrin (*FLG*) mutations, expressed in the corneal epithelium. Loss of function of *FLG* alleles (R501X and 2282del4) were found in five KC cases, suggesting the role of FLG in pathogenesis.[41]

ZEB1 is a transcription factor that has a role on modulating epithelial-to-mesenchymal transition (EMT) and negative regulatory binding sites on IL2. Mutations in *ZEB1* are reported in patients with KC[42] and isolated patients (posterior polymorphous corneal dystrophy) with steep cornea without KC.[43] This indicates plausible association of ZEB1 in corneal diseases. Recently, a mutation altering the miR-184 seed region was reported in a family with KC and early-onset anterior polar cataract and KC.[44] This finding reveals the association of microRNA regulations in eye diseases.

Genome Wide Association Studies and KC

Multiple approaches have been used to identify common genetic factors that influence health and complex diseases. These include, whole-genome sequencing, whole-exome sequencing, targeted resequencing, and functional studies in transcriptome level. The genetic etiology of many complex diseases, including Fuchs' corneal dystrophies (FECD) and central corneal thickness, GWAS are useful tools to identify single nucleotide polymorphisms. The allele frequency differs significantly between cases and controls, which is taken into account in identifying the associated risk or protective nature of the genetic factors.[45],[46],[47] Recent GWAS reveals few candidate genes identified including *IL1B, CDH11, NUB1, COL27A1*, and hepatocyte growth factor (HGF) *RAB3GAP1* and *LOX* which are associated with risk factor for KC. Interleukin 1 (IL1) released and triggered by the corneal epithelial cell during keratocyte apoptosis has been reported in 60% keratoconic cornea.[48],[49],[50],[51] The guanosine triphosphatase (GTPase)

activating protein subunit 1 (*RAB3GAP1*) gene mutations have been previously reported to be associated with Warburg Micro Syndrome with ocular disorders.[52] HGF expression in corneal keratinocytes is upregulated in response to corneal injury, which has binding site for proinflammatory cytokine IL-6, which is elevated in KC patients.[53] The association of HGF with KC suggests the potential involvement of inflammatory pathway, moreover it has been shown as a risk factor for refractive error in several populations including Han Chinese and Caucasians.[54],[55] Lu and colleagues recently identified multiple loci associated with central corneal thickness (CCT) and KC. GWAS further showed that two CCT-associated loci, *FOXO1* and *FNDC3B*, conferred relatively large risks for KC.[56] Recently, nonparametric linkage analysis identified a substitution at *IL1RN* and deletion at *SLC4A11* that segregated with phenotype in familial KC in Ecuadorian origin.[57] *IL1RN* gene, member of cytokine family and modulator inflammatory response, mutations in *SLC4A11*, which encodes a membrane-bound sodium-borate co-transporter associated with corneal endothelial dystrophy (CHED2) and Fuchs endothelial corneal dystrophy (FECD).[58]

So far genetic studies have suggested that KC has clinical variability and may be linked to multiple chromosomal regions, consistent with polygenic mode of inheritance. Despite several genomic loci, mutations were reported for disease susceptibility [Table 2], but lack of validation in larger numbers suggests genetic heterogeneity in KC.[2],[15] The whole-exome or genome sequencing and GWAS are significantly useful techniques, to explore novel genes and their functions in cellular pathways, which will provide the exact pathology of KC, thereby, aiding in designing better treatment modules. In example, *LOX* polymorphisms are associated with the treatment of collagen cross-linking to ensure that only "genotypically suitable" patients hopefully will undergo the gene-specific treatment, thus fulfilling the promise of personalized genomic medicine.[59]

Future Directions

Increasing our knowledge of genome sequence functionality will take us one step further in personalized medicine. These studies may enable prediction of genetic variant induced consequences beyond simple mapping for single nucleotide polymorphisms (SNPs). Emerging genomic approaches such as whole exome or genome sequencing will be very efficient to identify the disease causing mutations in families with KC.[56] However, the KC genetics and genomics approach is currently facing several challenges, including phenotype/genotype correlation, biological validation of variant function, and correlation with clinical interpretation. These challenges of genomic research pertain to all complex diseases like KC, making it imperative to stringently classify the KC stages and phenotypes. The emerging potential to subclassify clinical populations based on increasing number of disease trait phenotype (clinical study) and multi-omics study, offers new opportunity to dissect the genetic components of disease.

Finally, as the literature suggests, KC is a complex disorder and possibly involves multiple genes and various mechanisms that contribute to the clinical disease etiology. As such, devising a gene therapy strategy for this disease is fraught with risk and requires a better molecular understanding of the disease. However, certain genes such as *VSX1*, *DOCK9*, or *TGFB*1 may have an essential,[60] albeit sufficient role in the disease. Such a gene (or set of genes) delivered to the cornea via viral vectors[61] or nanoparticles[62] under the control of a cornea-specific promoter could hold promise for treatment. Alternatively, recent reports have claimed the disease to be driven by inflammation. A gene therapy strategy can therefore be envisaged in conjunction with anti-inflammatory treatment to obtain better results. Nonetheless, such gene therapy studies must be done in an appropriate tissue or animal model, a lack of which represents a very important hurdle currently.

In conclusion, both genetic and proteomic approaches together should provide further information on disease pathogenesis which can lead to better management of the disease.

Table 2: Candidate genes with mutations identified in patients with keratoconus

Genes	Physiological role
VSX1	Craniofacial and ocular development[21],[22],[23],[24]
SOD1	Major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals and provides a defense against oxygen toxicity (oxidative stress) [35],[36]
ZEB1	Modulating epithelial-to-mesenchymal transition (EMT) [43],[63]
TGFBI	It is a cytokine interacting with an extracellular matrix protein that plays a role in tissue injury and repair[29],[30]
MIR184	Expressed in the cornea and lens, 3'UTR of two target genes, INPPL1 (inositol polyphosphate phosphatase-like 1) and ITGB4 (integrin beta 4) while these two target genes are involved in corneal healing after injury[44]
COL4A3/ COL4A4	Corneal collagen structure, function and/or development during embryology[37],[38]
FLG	Apoptosis related, genetic risk factor for atopic dermatitis, with the protein expressed in the corneal epithelium[41]

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